CHRONIC TOXICITY SUMMARY

ACROLEIN

(2-propenal, acraldehyde, allyl aldehyde, acryl aldehyde)

CAS Registry Number: 107-02-8

I. Chronic Toxicity Summary

Inhalation reference exposure level	**0.06** m**g/m^3** (0.03 ppb)
Critical effect(s)	Histological changes in nasal epithelium in rats
Hazard index target(s)	Respiratory system; eyes

II. Physical and Chemical Properties (HSDB, 1995)

Description	Colorless or yellow liquid with piercing, disagreeable odor
Molecular formula	C_3H_4O
Molecular weight	56.1 g/mol
Density	0.843 g/cm^3 @ 20°C
Boiling point	53°C
Melting point	–88°C
Vapor pressure	220 torr @ 20°C
Odor threshold	160 ppb (370 µg/m^3) (Amoore and Hautala, 1983)
Solubility	Soluble in ethanol, diethyl ether, and up to 20% w/v in water
Conversion factor	1 ppm = 2.3 mg/m^3 @ 25° C

III. Major Uses or Sources

Acrolein is principally used as a chemical intermediate in the production of acrylic acid and its esters. Acrolein is used directly as an aquatic herbicide and algicide in irrigation canals, as a microbiocide in oil wells, liquid hydrocarbon fuels, cooling-water towers and water treatment ponds, and as a slimicide in the manufacture of paper (IARC, 1985). Combustion of fossil fuels, tobacco smoke, and pyrolyzed animal and vegetable fats contribute to the environmental prevalence of acrolein (IARC, 1985). Acrolein is a byproduct of fires and is one of several acute toxicants which firefighters must endure. It is also formed from atmospheric reactions of 1,3-butadiene. The annual statewide industrial emissions from facilities reporting under the Air Toxics Hot Spots Act in California based on the most recent inventory were estimated to be 54,565 pounds of acrolein (CARB, 2000).

IV. Effects of Human Exposure

Information regarding the chronic toxicity of acrolein to humans is scarce (IPCS, 1992). Acutely acrolein acts primarily as an irritant to the eyes and respiratory tract. The LOAEL for eye irritation is 0.06 ppm (0.14 mg/m^3) acrolein for five minutes (Darley *et al.*, 1960). In this study, 36 healthy human volunteers were exposed to 0.06 ppm (0.14 mg/m^3) for 5 minutes. Only volunteers without a prior history of chronic upper respiratory or eye problems were included in the study. Subjects wore carbon-filter respirators during exposure, so that only the eyes were exposed to the test mixture. Subjects reported a significant incidence of eye irritation in a questionnaire following the exposure.

V. Effects of Animal Exposure

Male Fischer-344 rats were exposed for 6 hours/day, 5 days/week for 62 days to acrolein at concentrations of 0, 0.4, 1.4, and 4.0 ppm (0, 0.92, 3.2, and 9.2 mg/m^3) (Kutzman, 1981; Kutzman *et al*., 1985). Each group of 24 animals was assessed for pulmonary function immediately prior to the end of the experiment. Pulmonary function tests (PFT) included lung volumes, forced respiratory capacity, pulmonary resistance, dynamic compliance, diffusing capacity of carbon monoxide, and multi-breath nitrogen washout. At the end of the experiment, animals were killed and histopathological changes in the lung were recorded. Eight additional rats were designated for histopathology and 8 rats were used for reproductive testing only. All analyses were performed post-exposure for 6 days to minimize the acute effects of acrolein. Mortality was high (56%) in rats exposed to 4.0 ppm (9.2 mg/m^3). The observed mortality was due to acute bronchopneumonia in these cases. The animals from this group that survived had reduced body weight. No histological changes were observed in extrarespiratory tissues in any group. There was a concentration-dependent increase in histological changes to the nasal turbinates and rhinitis, beginning at 0.4 ppm. Concentration-dependent damage to the peribronchiolar and bronchiolar regions was also observed. No lung lesions were observed in the 0.4 ppm group. The NOAEL for nasal lesions (squamous epithelial metaplasia and neutrophil infiltration) in this study was 0.4 ppm.

Feron *et al*. (1978) exposed groups of 20 Syrian golden hamsters, 12 SPF Wistar rats and 4 Dutch rabbits (of both sexes) to acrolein vapor at 0, 0.4, 1.4 and 4.9 ppm (0, 0.92, 3.2, and 11.3 mg/m^3) 6 h/day, 5 days/week for 13 weeks. The most important effects at the highest level included mortality in rats (3 of each sex), and ocular and nasal irritation, growth depression, and histopathological changes of the respiratory tract in each species. The changes in the airways induced by acrolein consisted both of destruction and of hyperplasia and metaplasia of the lining epithelium accompanied by inflammatory alterations. Rats were the most susceptible species examined and showed treatment-related histopathological abnormalities in the nasal cavity down to 0.4 ppm (LOAEL), whereas this level was a NOAEL in hamsters and rabbits. The results for individual rats at 0.4 ppm were not given.

The concentration required for depression of the respiratory rate of mice by 50% (RD_{50}) during 15 minutes of acrolein exposure was estimated as 1.7 ppm (Kane *et al.*, 1979). These authors proposed that the highest concentration suitable for a human air quality standard was 0.001 x

RD_{50}, or 0.002 ppm (0.005 mg/m^3). Buckley et al. (1984) investigated whether lesions occur in the respiratory tract of Swiss-Webster mice after exposure to the RD_{50} concentrations of ten sensory irritants including acrolein. After exposure of mice for 6 hr/day for 5 days to 1.7 ppm acrolein, the respiratory tract was examined for histopathologic changes. Acrolein (and all other irritants) produced lesions in the nasal cavity with a distinct anterior-posterior severity gradient. Acrolein specifically caused severe exfoliation and squamous metaplasia of the respiratory epithelium and moderate ulceration of the olfactory epithelium. Acrolein did not induce lesions in the lower respiratory tract.

Bouley *et al*. (1975,1976) exposed male SPF OFA rats continuously to 0.55 ppm (1.3 mg/m^3) of acrolein for up to 63 days. This level of acrolein led to a greater susceptibility to airborne *Salmonella enteritidis* infection during the first three weeks compared to control rats but it disappeared spontaneously when exposure was continued beyond three weeks. The general toxic effect of diminished weight gain (due to reduced feeding) compared to the control group lasted as long as exposure and disappeared only after acrolein was discontinued. Sneezing, a sign of nasal irritation, was consistently observed in the exposed animals on days 7 through 21 but ceased thereafter. No histopathology of the nasal cavity of or any other tissue was reported.

The pulmonary immunological defense against a bacterial challenge using *Staphylococcus aureus* in mice was impaired in a dose-dependent manner following exposure to acrolein at concentrations of 3 and 6 ppm (6.9 and 13.8 mg/m^3) for 8 hours (Astry and Jakab, 1983). In this study, the control exposure was not described.

Leach and associates (1987) found histological changes in pulmonary epithelium and mucosa in a group of 40 male Sprague-Dawley rats exposed to 3 ppm acrolein 6 hours/day, 5 days/week, for 3 weeks. Tests for pulmonary and systemic immune function revealed no significant differences between treated and control animals. Similarly, no difference was observed in survival from a bacterial challenge with *Listeria monocytogenes*, although this challenge was intravenous and not intratracheal, and may not have revealed the pulmonary macrophage impairment indicated by Astry and Jakab (1983).

Lyon and associates (1970) investigated the effects of repeated or continuous exposures of acrolein on Sprague-Dawley rats (n = 15/exposure group), guinea pigs (n = 15), Beagle dogs (n = 2), and male squirrel monkeys (n = 9). Animals were exposed intermittently to 0.7 or 3.7 ppm (1.6 or 8.5 mg/m^3) acrolein for 8 hours/day, 5 days/week, for 6 weeks, or continuously to 0.22, 1.0, or 1.8 ppm (0.5, 2.3, or 4.1 mg/m^3) for 90 days. Two monkeys in the 3.7 ppm intermittent exposure group died within 9 days. Monkeys and dogs salivated excessively during the first week. Squamous metaplasia and basal cell hyperplasia of the trachea were observed in monkeys and dogs; 7 of the 9 monkeys also exhibited bronchiolitis obliterans with squamous metaplasia in the lungs. Bronchopneumonia was noted in the dogs. Inflammation in the lung interstitiae was more prominent in the dogs than in the monkeys. Rats and guinea pigs did not exhibit signs of toxicity when exposed intermittently to 3.7 ppm. Continuous exposure to 1.0 and 1.8 ppm, but not 0.22 ppm acrolein, resulted in salivation and ocular discharge in the monkeys and dogs. Rats and guinea pigs appeared normal at all concentrations. Rats exhibited significant weight loss in the 1.0 and 1.8 ppm continuous exposure groups. Nonspecific inflammatory changes were observed in sections of brain, heart, lung, liver and kidney from all

species exposed to 1.8 ppm. The lungs from the dogs showed confluent bronchiopneumonia. Focal histological changes in the bronchiolar region and the spleen were detected at 0.22 ppm in dogs. Nonspecific inflammatory changes at the 0.22 ppm level were apparent in liver, lung, kidney and heart from monkeys, guinea pigs and dogs. Unfortunately the nasal cavity was not examined in this study. In addition there were no unexposed control animals for any species.

In one of the few chronic studies reported Feron and Kruysse (1977) exposed hamsters (18/gender) to 4 ppm (9.2 mg/m^3) acrolein for 7 hours/day, 5 days/week, for 52 weeks. Mild to moderate histological changes were observed in the upper and lower respiratory tract. No evidence of toxicity to other organs was apparent at necropsy, although body weight was decreased. Hematology, urinalysis, and serum enzymes were not affected by exposure. Thus 4 ppm is a chronic LOAEL for hamsters.

There are no reports of reproductive or developmental toxicity following exposure to acrolein. Kutzman (1981) found no significant changes in embryo viability in rats exposed to 4.0 ppm acrolein throughout pregnancy. Similarly, sperm morphology was reportedly not affected at this level. Bouley *et al*. (1975; 1976) exposed three male and 21 female SPF-OFA rats continuously to 0.55 ppm (1.26 mg/m^3) acrolein vapor for 25 days. The rats were allowed to mate on day 4 of the exposure. The number of acrolein-exposed pregnant rats and the number and mean body weight of their fetuses were similar to controls.

VI. Derivation of Chronic Reference Exposure Level

Study	Kutzman, 1981; Kutzman *et al*., 1985
Study population	Fischer-344 rats (24 males per group)
Exposure method	Discontinuous whole-body inhalation exposure of 0, 0.4, 1.4, and 4.0 ppm (0, 0.92, 3.2, and 9.2 mg/m^3)
Critical effects	Histological lesions in the upper airways
LOAEL	0.4 ppm (0.92 mg/m^3)
NOAEL	Not observed (see below)
Exposure continuity	6 hours per day, 5 days/week
Exposure duration	62 days
Average experimental exposure	0.071 ppm (0.16 mg/m^3) (0.4 x 6/24 x 5/7)
Human equivalent concentration	0.0087 ppm (gas with extrathoracic respiratory effects, RGDR = 0.14 based on MV = 0.18 m^3/day, SA(ET) = 11.6 cm^2)
LOAEL uncertainty factor	3 (see below)
Subchronic uncertainty factor	3 [62 days/(2x365) = 8.5% of lifetime]
Interspecies uncertainty factor	3
Intraspecies uncertainty factor	10
Cumulative uncertainty factor	300
Reference exposure level	0.03 ppb (0.06 μg/m^3)

The U.S. EPA (1995) based its RfC of 0.02 μg/m^3 on the same study but used a UF of 10 to "account for the lack of chronic studies." Based on OEHHA's methodology for chronic RELs (OEHHA, 2000), 62 days is 8.5% of 2 years and is just above the minimum length for a subchronic UF of 3. The LOAEL for nasal histological changes in rats was considered by U.S. EPA to be 0.4 ppm (0.92 mg/m^3). Only one rat showed slight metaplastic and inflammatory changes (see Figure 6 of Kutzman *et al*. (1985)), which would be insufficient to demonstrate a statistically significant increase. The potentially slight effect, however, was accounted for by use of only an intermediate LOAEL uncertainty factor of 3. OEHHA accepted U.S. EPA's interpretation.

For comparison with the proposed REL, a REL was estimated from the data of Feron *et al*. (1978) in rats, which found a LOAEL of 0.4 ppm after a 13 week exposure. Using time extrapolation and an RGDR of 0.18, U.S. EPA estimated a LOAEL (HEC) of 0.03 mg/m^3. Using UFs of 3 each for LOAEL to NOAEL, subchronic, and interspecies and of 10 for intraspecies variability (OEHHA, 2000) results in an estimated REL of 0.1 μg/m^3, slightly higher than the REL calculated from the data of Kutzman *et al*. (1985).

As another comparison, the data of Lyon *et al*. (1970) indicate that 0.22 ppm acrolein was a NOAEL and 1.0 ppm was a LOAEL for salivation and ocular discharge in squirrel monkeys exposed continuously for 90 days. Use of a subchronic UF of 10 (since squirrel monkeys have a lifespan of 15 to 25 years), an interspecies UF of 3 (since monkeys are primates), and an intraspecies UF of 10 (cumulative UF = 300) results in a REL estimate of 0.7 ppb (1.7 μg/m^3) for ocular discharge. Unfortunately no unexposed monkeys were studied which makes it difficult to evaluate the statements in the paper that "nonspecific inflammatory changes" (p. 730) and possibly "specific inflammatory changes" (p. 731) were present in sections of liver, lung, kidney and heart from the monkeys exposed to 0.22 ppm. In addition the study lasted less than 2% of a squirrel monkey's life span. The value of 0.7 ppb (1.7 μg/m^3) is also higher than OEHHA's acute REL of 0.19 μg/m^3 (OEHHA, 1999), which is based on an acute human study (Darley *et al*., 1960). In any case, the proposed chronic REL of 0.03 ppb (0.06 μg/m^3) should be protective of primates including man.

VII. Data Strengths and Limitations for Development of the REL

Significant strengths in the REL for acrolein include (1) the use of a well-conducted study with histopathological analysis and (2) the demonstration of consistent adverse effects among multiple studies of several species conducted by independent investigators.

Major areas of uncertainty are (1) the lack of adequate human exposure data, (2) limited reproductive toxicity data, (3) the absence of a definite NOAEL in the major study, and (4) the paucity of chronic inhalation exposure studies in both animals and humans.

VIII. References

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